and 6,054,439). Figures 19 and 20 of the specification clearly show a substantially better result when the protein effector and antisense oligonucleotide are used together than when either is used alone. The prior art patents previously mentioned, as well as U.S. Patent 6,066,625 (which uses the same oligonucleotide as the present specification) teaches those skilled in the art that antisense oligonucleotides against DNA methyltransferase used alone are effective in a mouse model. This model is predictive of success in humans (see paragraph 11-13 of the attached declaration of Dr. Jeffery Besterman, which was submitted in what is now U.S Patent No. 6,184,211). Thus, the present specification in view of the prior art does enable the claimed invention.

As to the mechanism of action of the combination, an inventor does not even have to know, nor teach how an invention works, only that it works. Figures 19 and 20 satisfy this requirement. In the present case, however, the oligonucleotide is working through an antisense mechanism (see the above-identified declaration at paragraphs11-13). Thus, one skilled in the art could follow the teachings of the specification and use the claimed invention without undue experimentation. As to dosage, pages 34 and 35 and Example 6 all give guidance as to the preferred dosages. Perhaps some experimentation would be required to optimize the dosage, such experimentation would not be undue.

Claims 1-3, 6 and 11-37 satisfy the written description requirement.

This rejection has been overcome by amendment in part and is traversed in part. Claims 4, 5, 38-41 and 46-50 have been canceled, so this rejection has been rendered moot as to those claims. Claims 1-3 have been amended to specify the human DNA methyltransferase gene. The previously cited patents would convey to one skilled in the art that the antisense component of the claimed invention works and Figures 19 and 20 would convey the same as to the combination. The statement by Dr. Branch that a "large number" of oligonucleotides would have to be screened to find out which ones work is simply incorrect (see paragraph 8 of the attached declaration of Dr. Moshe Szyf, which was submitted in what is now U.S. Patent No. 5,919,772). Further, it is not necessary to show all antisense oligonucleotides that work to show one of ordinary skill that the inventors possessed the claimed method at the time of filing,, particularly in view of the prior art which shows numerous operative embodiments. This is in contrast to Amgen. in which the entire sequence of the gene had to be known to make an operative embodiment.

For the reasons described above, Applicants respectfully submit that claims 1-3, 6 and 11-34 are now ready for allowance. If the Examiner believes that any discssion of this

communication would be helpful, she is invited to contact the undersigned by telephone at 781-933-6630.

Respectfully submitted,

Date: 13 August 2002

Wayne A. Keown
Reg. No. 33,923
500 West Cummings Park
Suite 1200
Woburn, MA 01801
781-938-1805 (Telephone)
781-938-4777 (Facsimile)

APPENDIX A: MARKED-UP CLAIMS AS AMENDED

1. (Amend d) A method for inhibiting the expression of a human DNA methyltransferase gene in a cell comprising contacting the cell with an effective synergistic amount of an antisense oligonucleotide which inhibits expression of the gene, and an effective synergistic amount of a protein effector of [a product of the gene] human DNA methyltransferase.

2. (Amended) A method for treating a disease responsive to inhibition of a human DNA methyltransferase gene [in a mammal] comprising administering to a [mammal, including a] human, which has at least one cell affected by the disease present in its body, a therapeutically effective synergistic amount of an antisense oligonucleotide which inhibits expression of the human DNA methyltransferase gene, and a therapeutically effective synergistic amount of a protein effector of [a product of the gene] human DNA methyltransferase.

3. (Amended) A method for inhibiting tumor growth in a [mammal] human comprising administering to a [mammal, including a] human, which has at least one neoplastic cell in its body, a therapeutically effective synergistic amount of an antisense oligonucleotide which inhibits expression of [a gene involved in tumorigenesis,] human DNA methyltransferaseand a therapeutically effective synergistic amount of a protein effector of [a product of the gene] human DNA methyltransferase.

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PENDING CLAIMS

1. (Amended) A method for inhibiting the expression of a human DNA methyltransferase gene in a cell comprising contacting the cell with an effective synergistic amount of an antisense oligonucleotide which inhibits expression of the gene, and an effective synergistic amount of a protein effector of human DNA methyltransferase.

2. (Amended) A method for treating a disease responsive to inhibition of a human DNA methyltransferase gene comprising administering to a human, which has at least one cell affected by the disease present in its body, a therapeutically effective synergistic amount of an antisense oligonucleotide which inhibits expression of the human DNA methyltransferase gene, and a therapeutically effective synergistic amount of a protein effector of human DNA methyltransferase.

3. (Amended) A method for inhibiting tumor growth in a human comprising administering to a human, which has at least one neoplastic cell in its body, a therapeutically effective synergistic amount of an antisense oligonucleotide which inhibits expression of human DNA methyltransferaseand a therapeutically effective synergistic amount of a protein effector of human DNA methyltransferase.

Claim Cancelled

Problem

6. The method of claim 5, wherein the protein effector is selected from the group consisting of 5-aza-cytidine, 5-aza-2'-deoxycytidine.

11. The method of claim 1, 2 or 3, wherein the antisense oligonucleotide has at least one internucleotide linkage selected from the group consisting of phosphorothioate, phosphorodithioate, alkylphosphonate, alkysphosphonothioate, phosphortriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleotide linkages.

12. The method of claim 1, 2 or 3, wherein the antisense oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region and an alkylphosphonate or alkylphosphonothioate region.

13. The method of claim 1, 2 or 3, wherein the antisense oligonucleotide comprises a ribonucleotide or 2'-O-substituted ribonucleotide region and a deoxyribonucleotide region.

14. The method of claim 1, wherein said cell is contacted with an effective synergistic amount of at least one antisense oligonucleotide for an effective period of time.

15. The method of claim 2 or 3, wherein the mammal is administered a therapeutically effective synergistic amount of at least one antisense oligonucleotide for a therapeutically effective period of time.

16. The method of claim 1, wherein said cell is contacted with an effective synergistic amount of at least one protein effector for an effective period of time.

17. The method of claim 2 or 3, wherein the mammal is administered a therapeutically effective synergistic amount of at least one protein effector for a therapeutically effective period of time.

18. The method of claim 1, wherein each of the antisense oligonucleotide and the protein effector is admixed with a pharmaceutically acceptable carrier prior to contacting the cell.

19. The method of claim 2 or 3, wherein each of the antisense oligonucleotide and the protein effector is admixed with a pharmaceutically acceptable carrier prior to administration to the mammal.

20. The method of claim 1, wherein the antisense oligonucleotide and the protein effector are mixed prior to contacting the cell.

21. The method of claim 2 or 3, wherein the antisense oligonucleotide and the protein effector are mixed prior to administration to the mammal.

22. The method of claim 1, wherein the cell is contacted separately with each of the antisense oligonucleotide and the protein effector.

23. The method of claim 22, wherein the cell is contacted with the antisense oligonucleotide prior to being contacted with the protein effector.

24. The method of claim 23, wherein the gene encodes a DNA methyltransferase and wherein the contacted cell is induced to undergo apoptosis or is arrested in the S phase of the cell cycle.

25. The method of claim 22, wherein the cell is contacted with the protein effector prior to being contacted with the antisense oligonucleotide.

26. The method of claim 25, wherein the gene encodes a DNA methyltransferase and wherein the contacted cell is arrested in the G_1 phase of the cell cycle.

27. The method of claim 2 or 3, wherein the antisense oligonucleotide and the protein effector are separately administered to a mammal.

28. The method of claim 27, wherein the antisense oligonucleotide is administered to the mammal prior to the administration of the protein effector.

29. The method of claim 28, wherein the gene encodes a DNA methyltransferase and wherein the cell in the mammal to which the antisense oligonucleotide is administered prior to the administration of the protein effector is induced to undergo apoptosis or is arrested in the S phase of the cell cycle.

30. The method of claim 27, wherein the protein effector is administered to the mammal prior to the administration of the antisense oligonucleotide.

31. The method of claim 30, wherein the gene encodes a DNA methyltransferase and wherein the cell in the mammal to which the protein effector is administered prior

to the administration of the antisense oligonucleotide is arrested in the G_1 phase of the cell cycle.

32. The method of claim 1, wherein the gene encodes a DNA methyltransferase and wherein the cell comprises a gene whose expression has been inactivated by methylation.

33. The method of claim 32, wherein expression of the gene whose expression has been inactivated by methylation is reactivated in the contacted cell.

34. The method of claim 32, wherein the gene whose expression has been inactivated by methylation is the $p16^{ink4P}$ tumor suppressor gene.